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Strained Heterocyclic Compounds. 8. Synthesis of *N*-[Bromo-(*t*-butyloxycarbonyl)phthalimidoacetyl]piperidine and Some Related Compounds and Their Reactions

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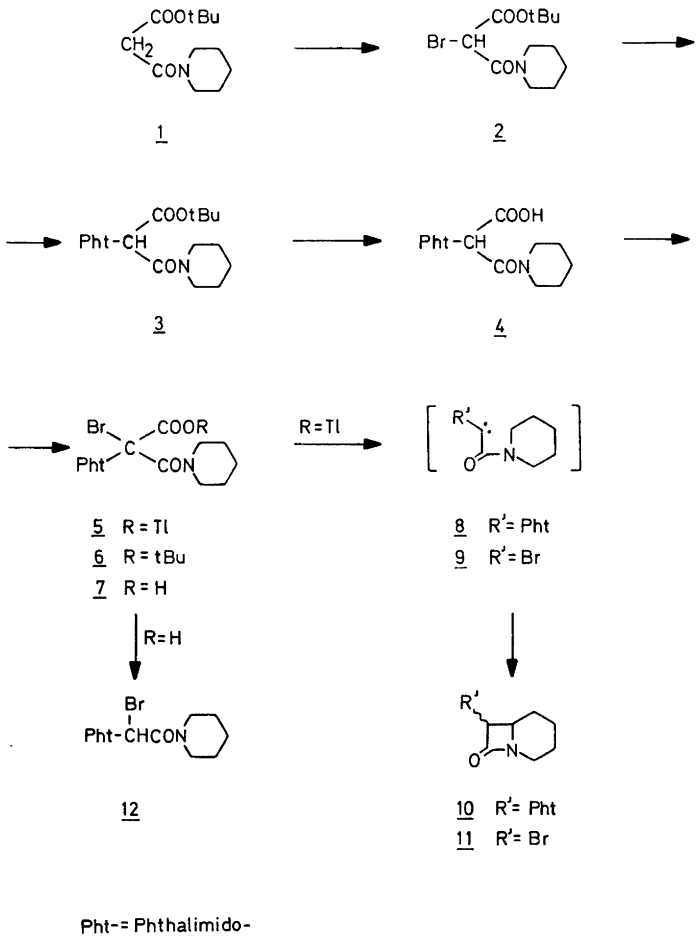
The thallium(I) salt of *N*-(bromocarboxyphthalimidoacetyl)piperidine (*5*) has been prepared. Decarboxylation in bromobenzene at 150 °C gave thallium bromide and a complex mixture of organic products. Only a trace of the desired phthalimido-β-lactam (*10*) was formed.

We have been interested in developing general methods for the synthesis of penicillin and cephalosporin analogues for some time. The main part of our early work was directed towards the construction of the appropriate β-lactam rings, by carbene insertion and we have synthesized fused α-halo-β-lactams [1] using this method. After considerable effort to replace the halogen in these β-lactams with an amide side chain, leaving the β-lactam intact, recently we were successful [2] in synthesising the phthalimido-β-lactam *10*. We have also investigated systems which would allow the introduction of the appropriate side chain prior to cyclization. The thallium(I) carboxylate *5* appeared to be a suitable intermediate for this purpose since it would be expected to yield a carbene on decarboxylation by analogy with other thallium [3] and mercury [4] salts of α-halocarboxylic acids.

The crude thallium salt *5* was prepared by the following reaction sequence. The carbodiimide promoted condensation of *t*-butyl hydrogen malonate and piperidine in a manner similar to that described by Brunwin *et al.*[5] gave the ester amide *1*. The yield was considerably improved by the use of dichloromethane as the solvent (65 % *vs.* reported yield of 15 %).[5] Bromination of *1* in chloroform solution, using acetamide as the hydrogen bromide acceptor,[6] gave a good yield of the monobromo compound *2*. This method should be of general value since the bromination of β-dioxocompounds frequently yields a mixture of mono- and dibromo derivatives. The compound *2* was converted to the phthalimido compound *3* by reaction with potassium phthalimide in DMSO or DMF solution. Hydrolysis with trifluoroacetic acid at 0 °C gave the acid *4* which was moderately stable in the solid state but decarboxylated in solution (*cf.* Sheehan *et al.*[7]). The acid *4* was added as a solid to a TFH solution containing the amount of thallium ethoxide required to convert it to the dithallium salt. On subsequent addition of one equivalent of bromine per mol of salt, approximately one equivalent of thallium bromide was precipitated, indicating that bromination had occurred. Filtration and evaporation of the solvent from the filtrate at 0 °C gave the crude thallium salt *5*, which tended to decompose on attempts at purification. The crude salt was dissolved in bromobenzene and heated to 150 °C. Rapid evolution of carbon dioxide and the precipitation of thallium(I) bromide indicated carbene formation. However, only traces of the desired phthalimido-β-lactam *10* could be detected in the reaction mixture by means of preparative TLC combined with mass spectrometry. A tarry residue was obtained on evaporation of the solvent and only small amounts of low molecular weight compounds could be isolated. The major isolable products, which were formed in yields of about 5 % each were phthalimidoacetylpiperidine, diphthalimidoacetylpiperidine, and phthalimide. The forma-



Pht-= Phthalimido-

tion of the latter two products indicates that partial elimination of thallium phthalimide takes place during the reaction. This leads to the formation of the bromo-β-lactam *11* which would react further to the phthalimido-β-lactam *10*.[2] Although the carbene *8* is probably formed, the traces of phthalimido-β-lactam observed may well be derived not from this but from the halo-β-lactam.

A different route to the thallium salt *5* was also investigated. The ester *3* was converted [8] to the bromoester *6*, which was hydrolyzed at −15 °C to the acid *7*. However, attempts to isolate this in a reasonably pure state failed due to its rapid decarboxylation to the compound *12* even at low temperature.

EXPERIMENTAL

All melting points were determined on a micro hot stage apparatus and are uncorrected. Elemental analyses were carried out by Centrala Analyslaboratoriet, Uppsala, Sweden and Mikroanalyslaboratoriet, Uppsala, Sweden. IR-spectra were recorded using a Perkin-Elmer Model 421 spectrophotometer, using KBr discs for solids and neat liquid films for oils. The numbers are given in cm^{-1}. NMR-spectra were recorded using a Varian A60 instrument, on $CDCl_3$ solutions except where otherwise stated. The chemical shifts are given as δ-values relative to TMS as internal standard. Mass spectra were recorded using an LKB 9000 instrument. Column chromatography was performed using silica gel (Merck 0.05 – 0.2 mm). Preparative thin layer chromatography was performed using silica gel (Merck Fertigplatten 2 mm). All THF used was

distilled from potassium metal/benzophenone in an N_2-atmosphere.

N-(t-Butoxycarbonylacetyl)piperidine (1). To a solution of crude *t*-butyl hydrogen malonate [5,9] (12 g, 0.075 mol) in dry dichloromethane (75 ml) cooled to 0 °C was added freshly distilled piperidine (6.4 g, 0.075 mol). The mixture was stirred and cooled for 15 min. A solution of dicyclohexylcarbodiimide (15 g, 0.075 mol) in dry dichloromethane (50 ml) was then added dropwise during 1/2 h, the mixture being held at 0 °C. After an additional period of stirring at room temperature for 3 h the dicyclohexylurea formed was filtered off. Unreacted dicyclohexylcarbodiimide was destroyed by adding 2 M HCl dropwise to the cooled filtrate and the mixture was filtered again. The filtrate which was two-phased was separated into organic and aqueous phases. The aqueous phase was extracted with 2 portions of diethyl ether, the combined organic phases were extracted with an aqueous saturated $NaHCO_3$ solution and water, then dried over $CaCl_2$ and the solvent was evaporated. Distillation yielded *N*-(*t*-butoxycarbonylacetyl)piperidine (*1*) (11.0 g, 65 %) b.p. 124 °C/0.5 mmHg.

N-[Bromo(t-butoxycarbonyl)acetyl]piperidine (2). *N*-(*t*-butoxycarbonylacetyl)piperidine (1.6 g, 7 mmol) and acetamide (0.83 g, 14 mmol) were refluxed in dry chloroform (25 ml) and a solution of bromine (1.1 g, 7 mmol) was added dropwise through the condenser. After 1/2 h the acetamide-hydrobromic acid complex[6] was filtered off, the filtrate was washed with one portion of an aqueous $Na_2S_2O_4$ solution and one portion of water, then dried over $CaCl_2$ and the solvent was evaporated. Chromatography using silica gel (110 g SiO_2/2 g crude product) with light petroleum (b.p. 40–60 °C) containing increasing amounts of diethyl ether as the eluent gave 1.5 g (70 %) of *N*-[bromo(*t*-butoxycarbonyl)acetyl]piperidine (*2*) as a colourless oil. An analytical sample was purified by preparative TLC using distilled diethyl ether as eluent. (Found: C 47.2; H 6.6; N 4.3; Br 26.1. Calc. for $C_{12}H_{20}NO_3Br$: C 47.1; H 6.6; N 4.6; Br 26.1). IR: 1750, 1730 C=O; 1650 C=O. NMR: 1.40 [s, 9 H, OC(CH_3)$_3$]; 1.62 (s, 6 H, CH_2); 3.48 (s, 4 H, N-CH_2); 5.03 (s, 1 H, CHBr). MS: *m/e* 249, 251 (M−C_4H_8), 226 (M−Br) 170 (M−C_4H_8Br), 112, 84.

N-(t-Butoxycarbonylphthalimidoacetyl)piperidine (3). *N*-[Bromo(*t*-butoxycarbonyl)acetyl]-piperidine (0.5 g, 1.63 mmol) and potassium phthalimide (0.3 g, 1.63 mmol) were heated in 30 ml freshly distilled DMSO at 50 °C for 1 1/2 h. The solvent was evaporated *in vacuo* and the reaction mixture was dissolved in chloroform, washed with water, then dried over $CaCl_2$ and the solvent was evaporated. Column chromatography using silica gel with diethyl ether as eluent gave 0.48 g (79 %) of (*3*) m.p. 132–134 °C (dec.). (Found: C 64.3; H 6.5; N 7.4. Calc. for $C_{20}H_{24}N_2O_5$: C 64.5; H 6.5; N 7.5). IR: 1770, 1730 >C=O, 1660 >C=O. NMR 1.52 [s, 9 H, −OC(CH_3)$_3$]; 1.66 (s, 6 H, -CH_2-); 3.4–3.9 (s, 4 H, N-CH_2); 5.65 (s, 1 H, Pht-CH); 7.78 (m, 4 H, aromatic protons). MS: *m/e* 372 (M); 316 (M−C_4H_8), 272 (M−$C_5H_4O_2$).

N-[Bromo(t-butyloxycarbonyl)phthalimidoacetyl]piperidine (6). To a suspension of 0.93 g (0.018 mol) of sodium hydride (50 % dispersion in oil) in 250 ml of dry THF was added in portions 6.8 g (0.018 mol) of *3*. The reaction mixture was refluxed for 1 h, then cooled to 0 °C in an icebath. A cooled solution of 2.9 g (0.018 mol) of bromine in 25 ml of dry dichloromethane was added rapidly dropwise. The solution was washed with one portion of an aqueous $Na_2S_2O_4$ solution, one portion of water, then dried over $CaCl_2$ and the solvent was evaporated. The crude product was crystallized from dichloromethane/diethyl ether to give 5.4 g (66 %) of *4*, m.p. 150–152 °C (dec.). A second crop of crystals was obtained, weighing 0.9 g (11 %). (Found: C 53.2; H 5.25; N 6.15; Br 17.9. Calc. for $C_{20}H_{23}N_2O_5Br$: C 53.2; H 5.14; N 6.2; Br 17.7). IR: 1790, 1760, 1735 >C=O; 1650 >C=O. NMR: 1.5 [s, 9 H, OC(CH_3)$_3$]; 1.66 (s, 6 H, -CH_2-); 3.4–3.9 (s, 4 H, N-CH_2); 7.85 (m, 4 H, aromatic protons). MS: *m/e* 394, 396 (M−C_4H_8), 371 (M−Br), 349, 351 (M−$C_5H_9O_2$), 112, 84.

N-(Carboxyphthalimidoacetyl)piperidine (4). *N*-(*t*-Butoxycarbonylphthalimidoacetyl)piperidine (0.37 g, 0.001 mol) was stirred in 5 ml of trifluoroacetic acid at 0 °C for 1/2 h. Evaporation of the TFA *in vacuo* and crystallization of the residue from cold, dry diethyl ether gave crystals of *N*-(carboxyphthalimidoacetyl)piperidine (0.25 g, 79 %) m.p. 88–90 °C (dec.). (Found: C 60.8; H 5.2; N 8.8. Calc. for $C_{16}H_{16}N_2O_5$: C 60.8; H 5.1; N 8.9). IR: 3200–2800 (broad)-OH, 1770, 1740, 1715 >C=O, 1610 >C=O. NMR: (DMSO) 1.55 (s, 6 H, CH_2); 3.40 (s, 4 H, N-CH_2); 5.76 (s, 1 H: Pht-CH); 7.83 (s, 4 H, aromatic protons). MS, *m/e* 316 (M), 272 (M−CO_2), 112, 84.

Hydrolysis of 6 *to* N-*(bromophthalimidoacetyl-piperidine (12).* Compound *6* (0.45 g, 0.001 mol) was stirred in 10 ml of trifluoroacetic acid at room temperature for 10 min. The solvent was evaporated and the product was dissolved in chloroform, washed with water, then dried over $CaCl_2$ and the solvent was evaporated. Crystallization of the residue from dichloromethane/diethyl ether gave 0.29 g (82 %) of *N*-(bromophthalimidoacetyl)piperidine m.p. 105–107 °C. (Found: C 51.4; H 4.33; N 7.92; Br 23.0. Calc. for $C_{15}H_{15}N_2O_3Br$: C 51.4; H 4.32; N 7.98; Br 22.7). IR: 1790, 1770, 1725 >C=O; 1655 >C=O. NMR: 1.57 (s, 6 H, CH_2); 3.5 (s, 4 H, N-CH_2); 6.76 (s, 1 H, -CHBr-); 7.82 (m, 4 H, aromatic protons). MS: *m/e* 350, 352 (M), 271 (M−Br), 112, 84.

Preparation and decomposition of 5. *N*-(Carboxyphthalimidoacetyl)piperidine (*4*) (0.632 g, 2 mmol) was added to a solution of 1.00 g (4 mmol) of thallium(I) ethoxide in THF (30 ml) at room temperature. The mixture was

cooled to 0 °C and an ice-cold solution of 0.32 g (2 mmol) of bromine in dry dichloromethane was added dropwise. The yellowish precipitate of thallium(I) bromide (0.49 g, 86 %) was removed by filtration and the solvent from the filtrate was evaporated *in vacuo*. Dry bromobenzene (25 ml) was added to the residue and the solution was refluxed for 1/2 h. After that period of time the gas evolution accompanying refluxing was observed to cease. The precipitate of thallium(I) bromide (0.505 g, 89 %) formed was removed by filtration and the solvent from the filtrate was evaporated. The residue contained a large number of products the separation of which was accomplished by preparative TLC. Those products identified were phthalimide (~4 %), *N*-(phthalimidoacetyl)piperidine (~5 %), *N*-(diphthalimidoacetyl)piperidine (~5 %), and traces of 7-phthalimido-8-oxo-1-azabicyclo[4.2.0]octane (*10*).

N-(Diphthalimidoacetyl)piperidine. *N*-(Dibromoacetyl)piperidine (0.7 g, 2.5 mmol) and potassium phthalimide (1.1 g, 6 mmol) were refluxed in freshly distilled dimethylformamide (20 ml) for 1 h, after which period the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with water, then dried over $CaCl_2$ and the solvent was evaporated. Purification of the residue on a column of silica gel eluted with diethyl ether gave *N*-(diphthalimidoacetyl)piperidine (0.371 g, 37 %).[10] An analytical sample was obtained by recrystallization from chloroform/diethyl ether. M.p. 247 – 249 °C. (Found: C 65.9; H 4.7; N 9.7. Calc. for $C_{23}H_{19}N_3O_5$: C 66.2; H 4.58; N 10.1). IR: 1780, 1765, 1720 >C=O; 1655 >C=O. NMR: 1.55 (s, 6 H, $-CH_2-$); 3.21 (s, 2 H, N-CH_A); 3.57 (s, 2 H, N-CH_B); 6.70 (s, 1 H, -*CH*); 7.65 (m, 8 H, aromatic protons). MS: *m/e* 417 (M), 306 (M – C_6H_9NO), 112, 84.

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REFERENCES

1. a. Johansson, N. G. and Åkermark, B. *Acta Chem. Scand. 25* (1971) 1927; b. Johansson, N. G. *Acta Chem. Scand. 27* (1973) 1417; c. Johansson, N. G. and Åkermark, B. *Tetrahedron Lett.* (1971) 4785; d. Åkermark, B., Byström, S., Florin, E., Johansson, N. G. and Lagerlund, I. *Acta Chem. Scand. B. 28* (1974) 375.
2. a. Åkermark, B., Lagerlund, I. and Lewandowska, J. *Acta Chem. Scand. To be published*; b. Lagerlund, I. *Manuscript in preparation.*
3. Moss, R. A. *Chem. Eng. News. 47* (1969) 60.
4. Robson, R. and Dickson, I. E. *J. Organometal Chem. 15* (1968) 7.
5. Brunwin, D. M., Lowe, G. and Parker, J. *J. Chem. Soc. C* (1971) 3756.
6. Zeile, K. and Meyer, H. *Ber. Deut. Chem. Ges. 82* (1949) 275.
7. Sheehan, J. C. and Schneider, J. A. *J. Org. Chem. 31* (1966) 1635.
8. Stotter, P. L. and Hill, K. A. *Tetrathedron Lett.* (1972) 4067.
9. Backer, H. J. and Homan, J. D. H. *Rec. Trav. Chim. Pays-Bas 58* (1939) 1048.
10. The yield has not been optimized.

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